REGULATORY APPROVALS

PLAYING EPO-LITICS AT THE FDA

NEW YORK—Heads normally don't turn just because the Food and Drug Administration (FDA, Bethesda, MD) postpones an advisory committee meeting. But with issues of orphan drug status and windfall reimbursements swirling around Capitol Hill this session, the rescheduling of the June 29 Blood Products Advisory Committee meeting to hear data on erythropoietin (EPO) created a stir. And lost in the controversy is the fact that the FDA is attempting to address a very real scientific issue—when and how the sugar structures of protein therapeutics make a difference.

Some observers are not so much asking why the meeting was postponed as why it was called to begin with. The intention was to have Amgen (Thousand Oaks, CA), Upjohn (Kalamazoo, MI), and Johnson & Johnson (J&J, New Brunswick, NJ) all give testimony on the degree of difference between the EPO products of Amgen and Genetics Institute (GI, Cambridge, MA). Amgen and J&J are partners, and GI has licensed its EPO to a collaboration between Upjohn and Chugai (Tokyo). Amgen's has been approved for marketing by the FDA for a year while the GI product awaits final review. Amgen also holds orphan drug status on its indication, and is making whopping profits in a protected market. (The other side has filed a Citizen's Petition claiming, among other things, that the patient population for Amgen's indication—end-stage renal failure—is no different than chronic renal failure, which exceeds 200,000 patients.) As well, as any biotech-watcher knows, the two sides are embroiled in a testy patent battle (see, e.g., *Bio/Technology* **8**:172, Feb. '90) over who has the legal right to make EPO in the U.S. The Chugai-Upjohn/GI team is arguing that they hold a valid patent, and the House Committee Report on the 1985 amendments to the Orphan Drug Act specifies that the Congressional intent was not to override patent law provisions.

Stock analyst Teena Lerner (Shearson Lehman Hutton, New York) described the meeting as "political in nature, though cloaked in the aura of science...We know of no previous FDA advisory committee meeting with such an agenda"—namely, asking scientists to distinguish between two products under the provisions of the Orphan Drug law. Stuart Weisbrod of Prudential Bache (New York) points out that, if the GI product is approved and differentiated from Amgen's molecule, other hormones would follow through the FDA, in particular Serono's (Norwell, MA) human growth hormone (hGH) variant. Its sugar structure differs from that of Eli Lilly's (Indianapolis, IN) hGH product, which for years has enjoyed orphan drug status. Lilly would like to hold onto its market exclusivity, and may be pressuring the Bush Administration to make FDA drag its feet on EPO (Bush is an ex-director of Lilly). Or so that line of reasoning goes. And approvals of any drugs that compete with existing orphan products would spur competition and, presumably, price-cutting, thereby lowering reimbursement costs.

The FDA's reasons for postponing the meeting make sense, however, without these Machiavellian undercurrents. The agency wants to hold its meeting in conjunction with an Institute of Medicine (IOM) conference planned for late October that will discuss micro-heterogeneity in macromolecules. The agency then would have the opportunity to invite many leading authorities in attendance at the IOM meeting to discuss EPO in a broader context. It also notified the parties to the June 29 meeting that some experts it wanted on hand had scheduling conflicts.

"The scientific questions are anything but trivial," notes Stanford University's (CA) Charles Goochee. "From a purely scientific point of view, it's clear that glycosylation can affect solubility, thermal stability, resistance to protease attack, protein folding and secretion, protein conformation, specific activity, clearance rate, and antigenicity." EPO is 40–50 percent carbohydrate, with three N-linked oligosaccharides and one O-linked oligosaccharide. Its clearance rate is sensitive to terminal sialic acid and may also be affected by the oligo structure in general, as is specific activity. And thermal stability is "clearly demonstrated" to be sensitive to the oligo structure, Goochee points out.

"Given the sensitivity of these several properties of EPO to oligosaccharides, the questions the FDA is raising are both appropriate and non-political," Goochee believes. But while politics were not part of FDA's asking these questions, they did enter the picture later. **—Mark Ratner**